Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 for lack of utility. Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". For the reasons outlined below, Applicants respectfully disagree.

Applicants respectfully maintain that utility for PRO830 polypeptides and antibodies thereof is based on the observed 2.188 fold to 2.549 -fold amplification of the DNA encoding PRO830 in lung tumors. Detecting the presence or absence of PRO830 polypeptides, using antibodies, would be useful in the diagnosis of lung cancer and such a utility would be evident to one skilled in the art based on the data presented in the specification. Applicants present reasons for their position below.

The Examiner alleges that the instant application does not disclose a biological role for the PRO830 protein and antibodies thereof but acknowledges that the specification shows that gene expression is increased in tumor cell lines and primary tumors. The Examiner does not accept the teachings of the Polakis nor the Ashkenazi declaration and maintains that it does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state. The Examiner says that "it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and protein levels" and quotes references like Hu, Hancock and Wang to indicate that "literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue". Regarding Orntoft et al., Hyman et al. and Pollack et al. the Examiner rejects these references since they allegedly do not look at a single gene at a time and therefore do not support utility of the claimed proteins. The Examiner further does not

accept utility for PRO830 based on homology to known proteins and quotes Doerks et al., Brenner et al., and Bork et al. to support this rejection.

For the reasons outlined below, Applicants respectfully disagree.

Arguments

Initially, without acquiescing to the propriety of the rejection and without prejudice to pursuing the subject matter in latter applications, Applicants submit that they do not claim utility for PRO830 polypeptides and antibodies thereof based on its homology to known proteins in the instant application, and hence the rejections based on Doerks et al., Brenner et al., and Bork et al. on protein homology should be withdrawn.

Regarding the rejection of the Polakis declaration since "the declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Applicants respectfully traverse this rejection and reproduce below, the entire paragraph with the relevant statement from Dr. Polakis' declaration so that the statement in question can be viewed in context:

> "Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4-5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that **for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell.** In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. **While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein"** (emphasis added).

Applicants further respectfully draw the Examiner's attention to the Utility Examination Guidelines, Part IIB, 66 Fed. Reg. 1098 (2001) which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being

questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statements in question from Dr. Polakis, an expert in the field, should be viewed in the context his statements regarding his personal research on human genes for which he isolated mRNA and studied the mRNA-protein correlations. For example, Dr. Polakis says:

> "In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, **we have identified approximately 200 gene transcripts** that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, **we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells**. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed" (emphasis added).

It is on the basis of his personal research that Dr. Polakis bases his viewpoint. As Dr. Polakis himself clearly acknowledges, exceptions to the central dogma exist, and he qualifies this statement in his declaration by saying:

> "While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Applicants submit that Dr. Polakis' statements would be considered reasonable and accurate by one skilled in the art, as required by the Utility guidelines, hence the Examiner's request for further evidentiary support is improper.

Regarding the Examiner's rejection based on Hu, and Hancock, Applicants discuss reasons below why these references do not support the Examiner's conclusions that "gene amplification does not necessarily result in increased protein levels."

For instance, the Hu et al. reference bases its conclusions on ***statistical analysis of information from published literature*** which is evidenced by its title: "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining" and by its statement: "We have utilized a computational approach to *literature mining* to produce a comprehensive set of gene-disease relationships (emphasis added)." Further, Hu et al. state that they "compared the MedGene *breast cancer gene list* to a gene expression data set generated from *micro-array* analysis comparing *breast cancer and normal breast tissue samples*." (emphasis added; see page 408, right column). Therefore, Applicants submit that Hu's results were based on "statistical data," in which, by their own admittance, data had to be manipulated to "manage" the resulting outcome. For example, the authors admit, at least on page 406, right column, that "[i]nitial attempts at search the literature....revealed several sources of false positive and false negatives" which were "difficult to manage." Thus, to minimize such false positives, certain genes "had to be eliminated entirely, thereby reducing the false positive rate *but unavoidably underrepresenting some genes*" (emphasis added). Applicants submit that Hu's conclusions are based on statistical data rather than experimental (gene amplification) data presented in the instant application. While Hu's data could be useful for understanding gene relationships for a class of genes, for example, breast cancer genes, the Hu reference does not demonstrate that "gene amplification does not necessarily result in increased protein levels in general" because (1) it only studies gene relationships in breast cancer genes, and (2) because the results are generated through statistical analysis which was managed to "underpresent some genes." Therefore, the Examiner had not established that **it is more likely than not** that gene amplification does not necessarity result in increased protein levels in general by citing a reference that only discusses "breast cancer genes" while "underrepresenting some genes" and relies on "statistical data" for the same. Applicants further note that Hu et al. studied the relationship between mRNA and protein data. By relying

on Hu's mRNA-protein data for the instant rejection, it is noted that the Examiner inherently acknowledges the mRNA-protein relationship to gene amplification and so, for the same reasons, should rely on the Polakis declaration presented by the Applicants for support. In other words, it is therefore improper to reject the Polakis declaration "since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels."

Hence, reconsideration of the Polakis declaration, in view of these arguments is requested.

Regarding the rejection based on the Haynes et al. reference, once again draw the Examiner's attention to the data presented in the Haynes reference and corresponding interpretations thereof. Applicants respectfully point out that, Haynes found that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). That is, Haynes recognized that while there was a general trend of increased protein expression with increased mRNA levels, the Haynes reference teaches that protein levels (i.e. protein amounts) cannot accurately be predicted from mRNA levels or amounts, which is not the same as "no correlation between protein and mRNA". For example, even in Figure 1, Hayes shows that there was a *general* positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins even though the correlation is "not strictly linear" thereby not enabling one to accurately predict protein levels from mRNA levels. In fact, a careful look at Figure 1 of Haynes indicates that few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, contrary to the Examiner's position, the Haynes data actually supports the Polakis' statement that, in general, a positive correlation exists between mRNA and protein levels (even though the correlation may not be linear which prevents the data from being useful for accurately predicting protein levels from mRNA levels). In fact, the Haynes data meets the "more likely than not" utility standard since it studied **80 proteins** and showed "a general positive trend" or increase in protein levels for most of the 80 proteins with corresponding mRNA increases. Therefore, Applicants submit that the Haynes data indeed support the Polakis' declaration and

that the Examiner's rejection is based on a misrepresentation of the scientific data presented by Haynes *et al.*

Further, Applicants submit that the Hancock reference cited by the Examiner does not provide evidence for lack of utility. Hancock discusses the need for high-quality biomarkers in the genomics and proteomics era and the need for a "consensus-building process" and "consolidation of different lists of biomarkers". While the editorial indicates that the markers generated by proteomics are not always consistent with markers identified by expression profiling, which possibly reflects methodological differences between expression and proteomic studies, the statements in the editorial by no means provide evidence that Dr. Polakis' statements are not absolutely true. In fact, the statements in the editorial indicate the importance for proteomics (and protein markers generated thereof) in the third paragraph: "I think many people in the proteomics community would agree that federal granting agencies *should be enticed* to continue investments in basic proteomics technology." If anything, Hancock provides evidence that biomarkers like PRO830 and antibodies thereof are useful, and in fact desirable, provided there is a push towards a consolidated list of biomarkers (which is outside the scope of the utility requirement). Thus, Applicants respectfully point out that the Hancock reference in fact supports utility for protein markers despite seeming discrepancies between expression and proteomic studies.

Regarding the Ashkenazi declaration, Applicants submit that evidence regarding tumor classification and resulting treatment strategies for clinicians were discussed and presented in the reference Hanna and Mornin, submitted with the response filed July 20, 2004. This article taught that the HER-2/neu gene was shown to be amplified in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Even when the protein was not over-expressed, the information could lead to a more accurate classification of the cancer and a more effective treatment of it. Further, as discussed above for the Polakis declaration, Applicants submit that this rejection is improper under the Utility Examination Guidelines, Part IIB, 66 Fed. Reg. 1098 (2001). The Examiner cites the Wang reference to show that, "further action should be taken to characterize the functions of a particular gene of interest, including....validation for the importance of the gene in disease processes". Applicants have already submitted that they performed the necessary experiments to establish utility for PRO830 proteins and antibodies

thereof (gene amplification data) and further submit that, it is well- established under patent law that experiments done to reduce the invention to practice shows completion of invention and establishes its utility. That is, Applicants have asserted a role for PRO830 polypeptide as a protein marker, which can be detected, using the antibodies directed specifically against it, to diagnose lung cancer and its presence or absence would further assist in lung tumor classification.

Applicants submit that association for the PRO830 polypeptide and antibodies thereof with disease, namely, lung cancer, has been established based on the gene amplification results since the Examiner has not presented reference that meet the "more likely than not" standard set by the Utility Guidelines for patentable utility. Therefore, barring evidence to the contrary, that one skilled in the art would question such a correlation, utility for PRO830 has been established.

Taken together, Applicants submit that a *prima facie* case for lack of utility of the PRO830 polypeptide and antibodies thereof has not been established based on references Haynes, Hu, Hancock and Wang and a rejection of the Polakis and Ashkenazi declarations. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. §101 and §112, first paragraph be withdrawn.

Claim Rejections – 35 USC § 102

Claims 119-120, 122-124 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S.P.N. 5;169,933 (Anderson *et al.*) dated 1992. Applicants respectfully traverse this rejection.

As asserted in the previous response, Applicants submit only those antibodies that "specifically" bind to SEQ ID NO: 175 are encompassed by the instant claims. Accordingly, antibodies that bind to the Anderson sequence in addition to SEQ ID NO: 175 are not encompassed by the instant claims since they do not specifically bind to SEQ ID NO: 175. Therefore, the instantly claimed antibodies do not read on the Anderson claims. Accordingly, Applicants respectfully request that this rejection to the claims be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

Claims 119 and 124 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S.P.N. 5,169,933 (Anderson *et al.*) dated 1992 in view of U.S.P.N. 5,530,101 (Queen *et al.*). Applicants respectfully traverse this rejection.

As discussed above, the pending claims now recite "specifically binds" which only encompass those antibodies that specifically bind to SEQ ID NO: 175. Hence, the primary reference, Anderson falls as prior art and since Queen *et al.* does not teach the instantly claimed polypeptides and antibodies thereof, it falls as prior art too. Hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C10). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 8, 2005

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